

Figure 1

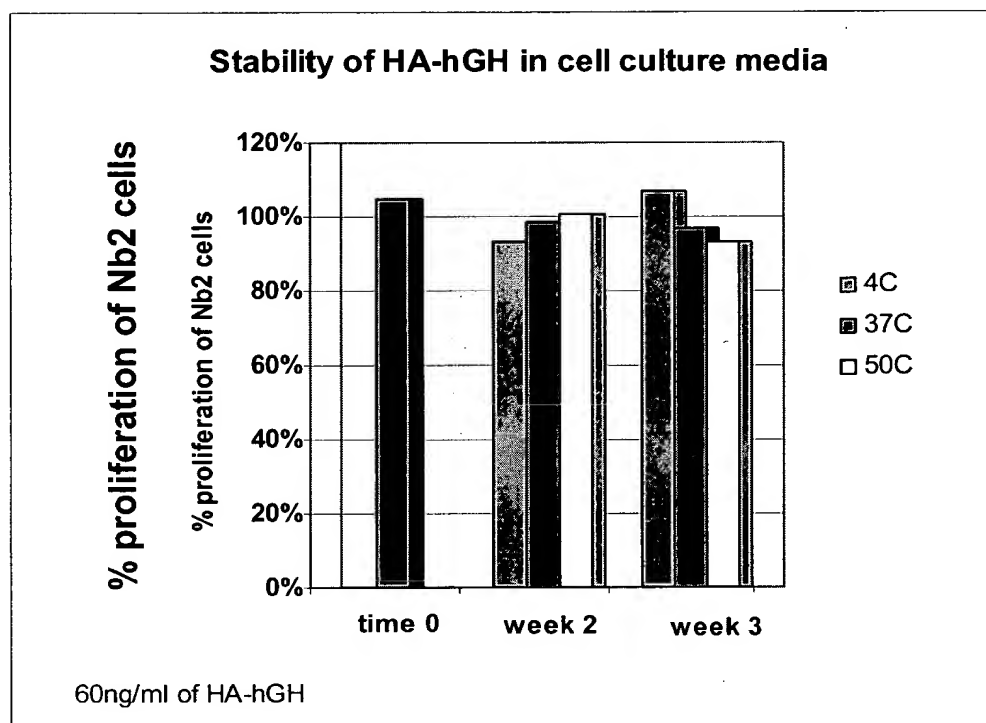


Figure 2

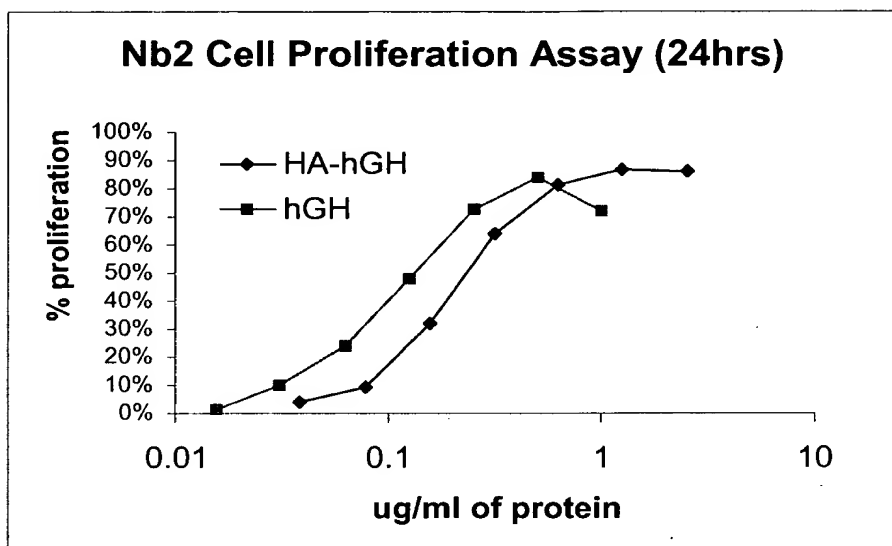
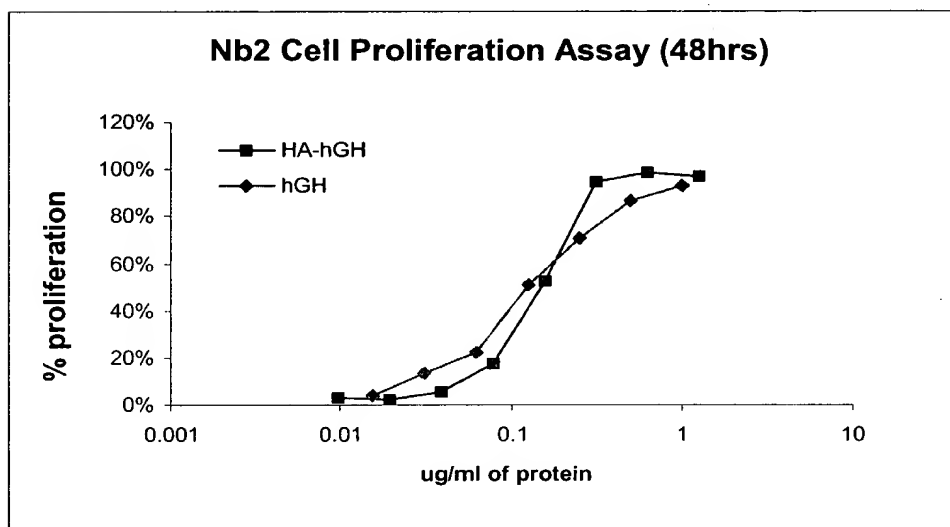
**Figure 3A****Figure 3B**



Figure 4

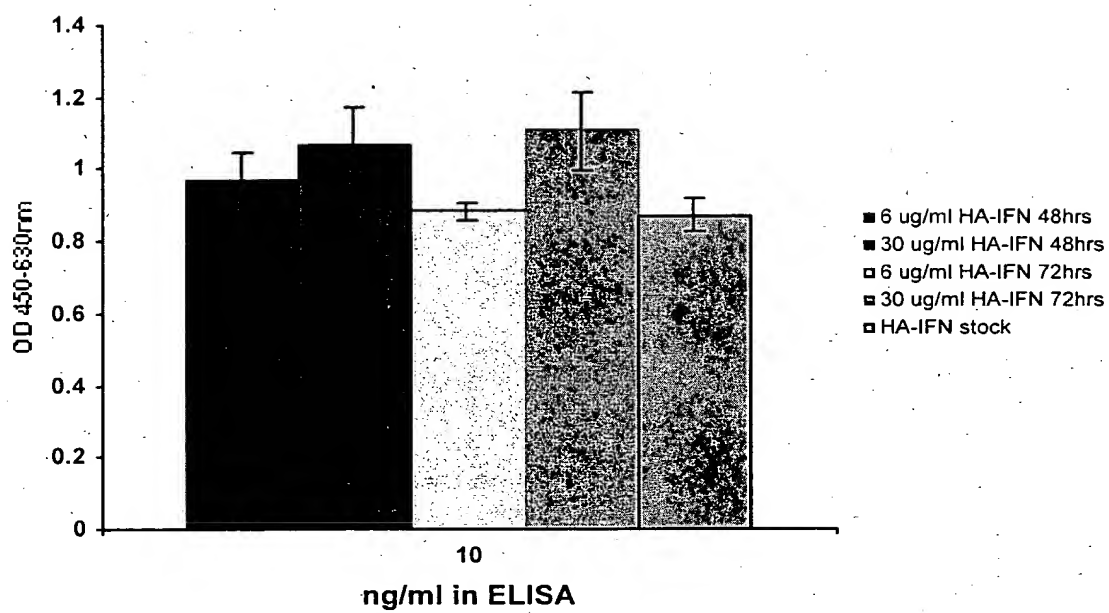


Figure 5

Figure 6

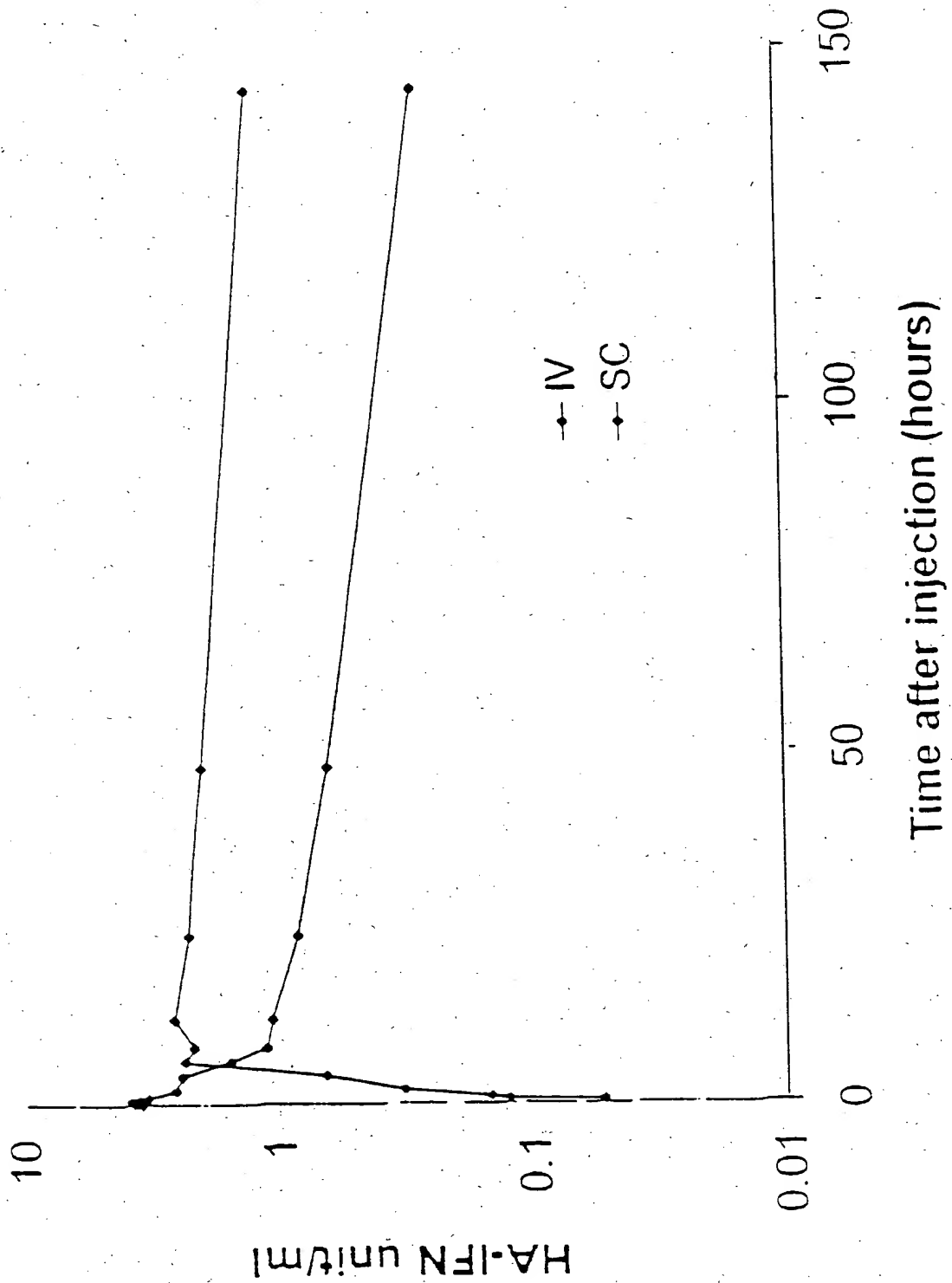
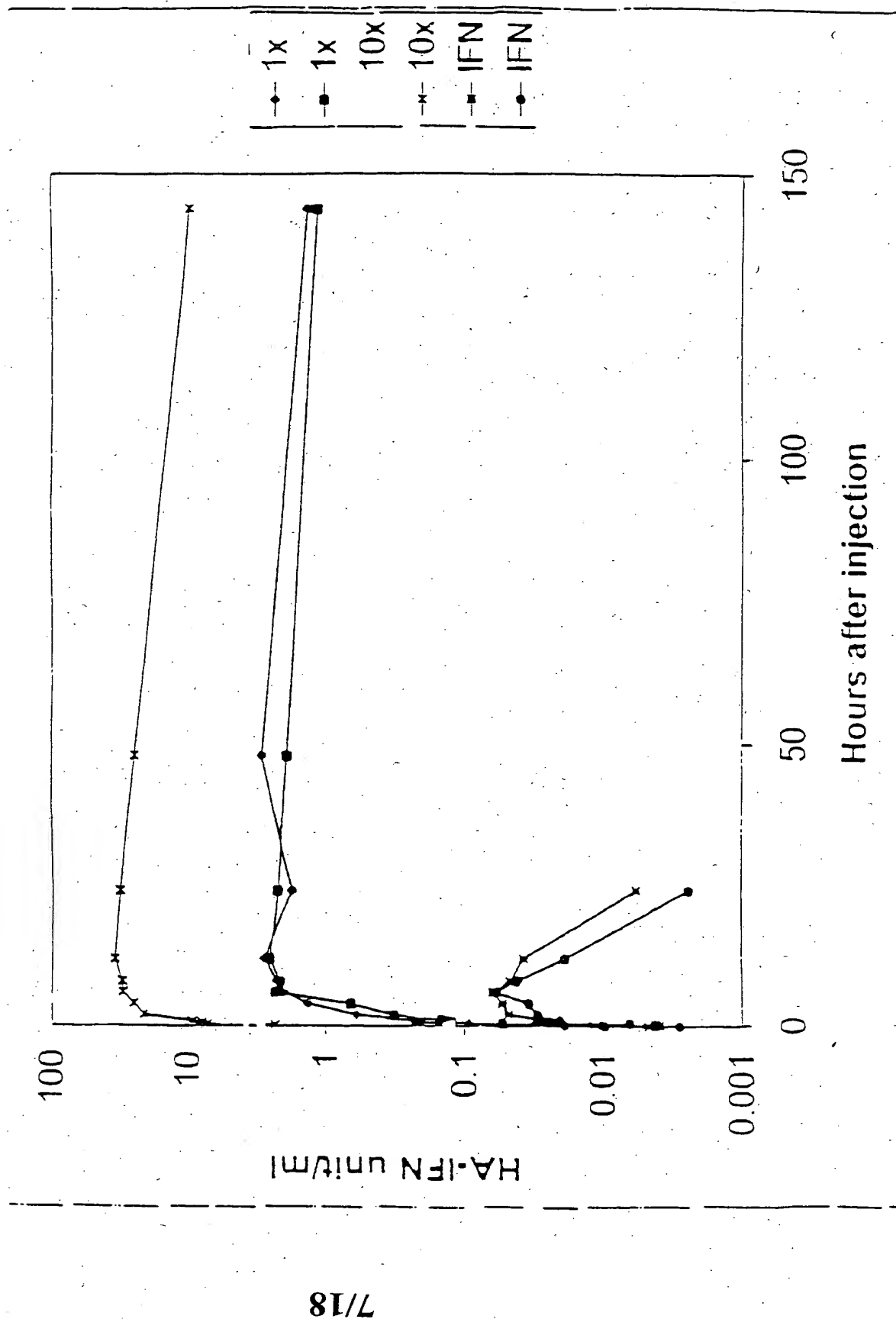


Figure 7



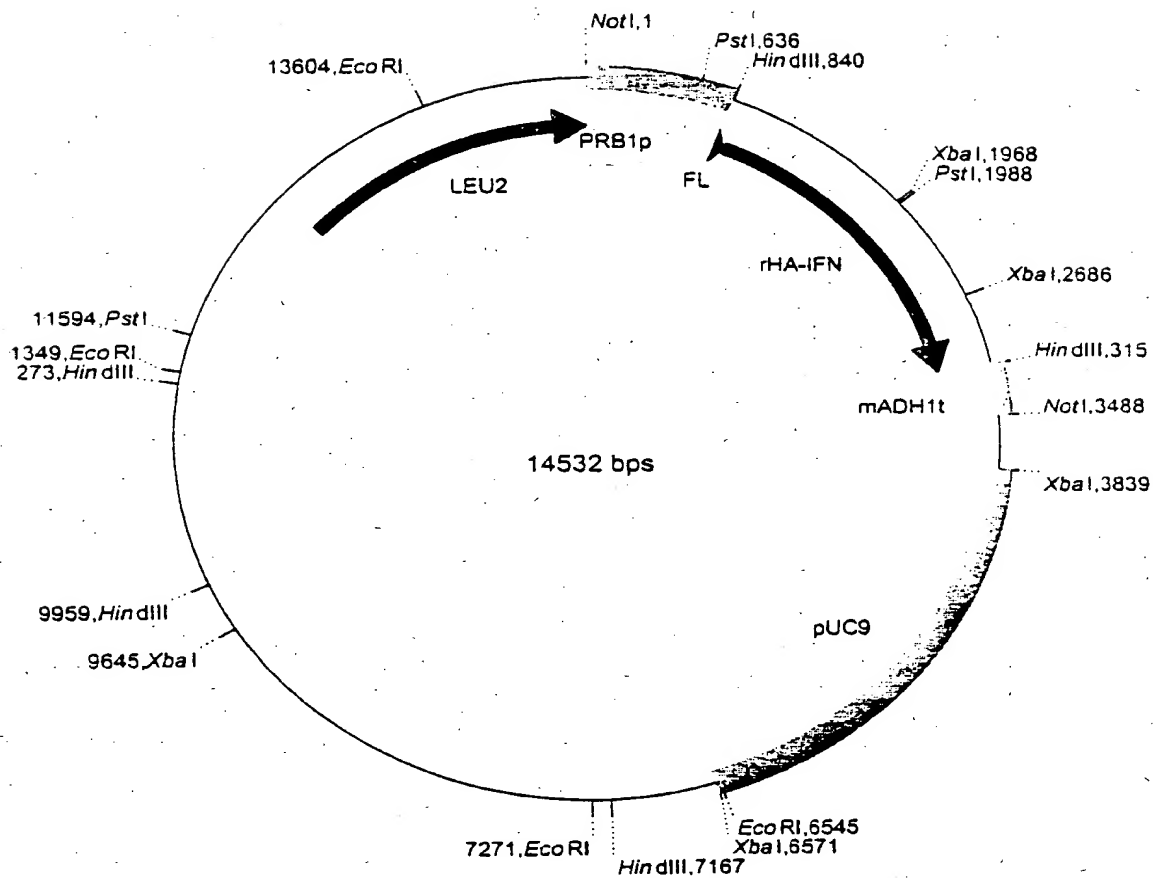


Figure 8. The HA-IFN α expression cassette in pSAC35. The expression cassette comprises
PRB1 promoter, from *S. cerevisiae*.
 Fusion leader, first 19 amino acids of the HA leader followed by the last 6 amino acids of the MF α -1 leader.
 HA-IFN α coding sequence with a double stop codon (TAATAA)
ADH1 terminator, from *S. cerevisiae*. Modified to remove all the coding sequence normally present in the *Hind* III/*Bam* HI fragment generally used.

Figure 8

1	DAHKSEVAHR HHHHH	FKDLGEENFK HHH	ALVLI AFAQY HHH HHHHHHHHHH	LQCCPFEDHV HHHHH	KLVNEVTEFA HHHHHHHHHH
	I		II		III
51	KTCVA <u>DES</u> AE NCDKSLHTLF HHHHH	GDKLCTVATL HHHHH	RETYGEMADC HHHH	CAKOE <u>PER</u> NE H HHHH	
101	CFLQHKKDDNP HHHH	NLPRLVRPEV H	DVMCTAFHDN HHHHHHHH	EETFLKKYLY HHHHHHHHH	EIARRHPYFY HHHHH
		IV			
151	APELLFFAKR HHHHHHHHHH	YKAAFTECCO HHHHHHHHH	AADKAACLLP HHHHH	KLDEL RDEGK HHHEHHHHHH	ASSAKQRLKC HHHHHHHHHH
			V		
201	ASLQKFGERA HHHHH	FKAWAVARLS HH	QRFPKAEFAE HH HHH	VSKLVTDLTK HHHHHHHHHH	VHTECC <u>H</u> GDL HHHHH HH
		VI		VII	
251	LECADDRADL HHHHHHHHHH	AKYIC <u>EN</u> ODS HHHHH	ISSKLKECCE HHHHH	KPLLEKSHCI HHHHHHH	AEVENDEMPA H
301	DLPSLAADFV HHHH	ESKDVCKNYA HHHHHH	EAKDVFLGMF HHHHHHH	LYEYARRHPD HHHHHH	YSVVL LRLA HHHHHHHH
		VIII			
351	KTYETTLEKC HHHHHHHHHH	CAAAD <u>P</u> HECY HH	AKVFDEFKPL H HHHHH	VEEPQNLIKQ HHHHHHHHHH	NCELFEQLGE HHHHHHH
			IX		
401	YKFQNAL LVR HHHHHHHHHH	YTKKVPQVST HHHH	PTLVEVSRNL H HHHHHHHHHH	GKVGSKCCKH HHH	PEAKRMPCAE HHHHHHHH
		X		XI	
451	DYLSVVLNQL HHHHHHHHHH	CVLHEKTPVS HHHHH	DRVTKCCTES HHHHHHHHH	LVNRRPPCFSA HHHHHHHH	LEVDETYVPK
501	EFNAETFTFH	ADICTLSEKE HHH HHH	RQIKKQTALV HHHHHMMEH	ELVKHKPKAT HHH	KEQLKAVMDD HHHHHHHH
		XII			
551	FAAFVEKCKK HHHHHHHHH	ADDKETCFAE HHHH	EGKKLVAAASQ HHHHHHHHHH	AALGL HH	

Figure 9

Examples of Modifications to Loop IV**a. Randomisation of Loop IV.**

IV

```

151  APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
      HHHHHHHHHH HHHHHHHHHH          HHHHH HHHHHHHHHHH HHHHHHHHHHH
  
```

IV

```

151  APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDEL RDEGK ASSAKQRLKC
      HHHHHHHHHH HHHHHHHHHH          HHHHH HHHHHHHHHHH HHHHHHHHHHH
  
```

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.

(X)_n



IV

```

151  APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
      HHHHHHHHHH HHHHHHHHHH          HHHHH HHHHHHHHHHH HHHHHHHHHHH
  
```

The insertion can be at any point on the loop and the length a length where n would typically be 6, 8, 12, 20 or 25.

Figure 10

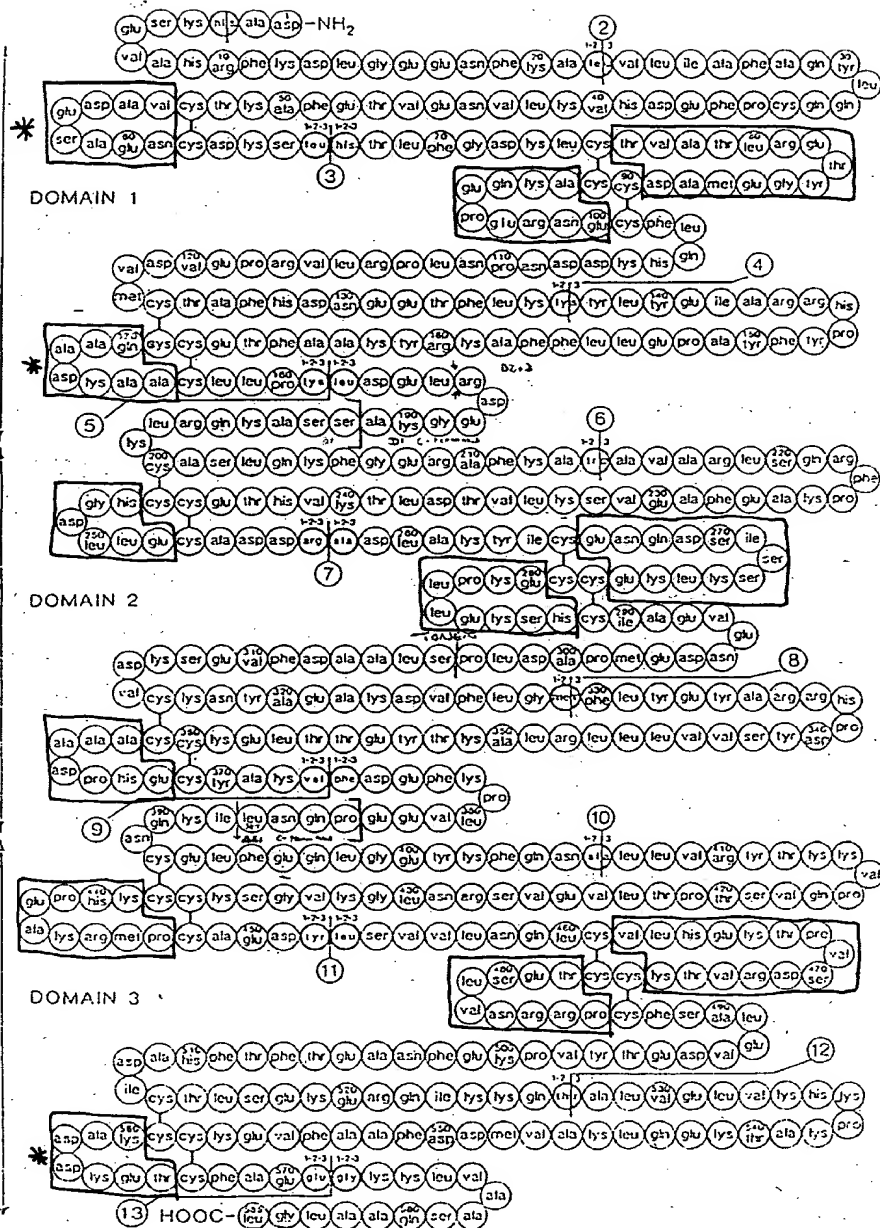
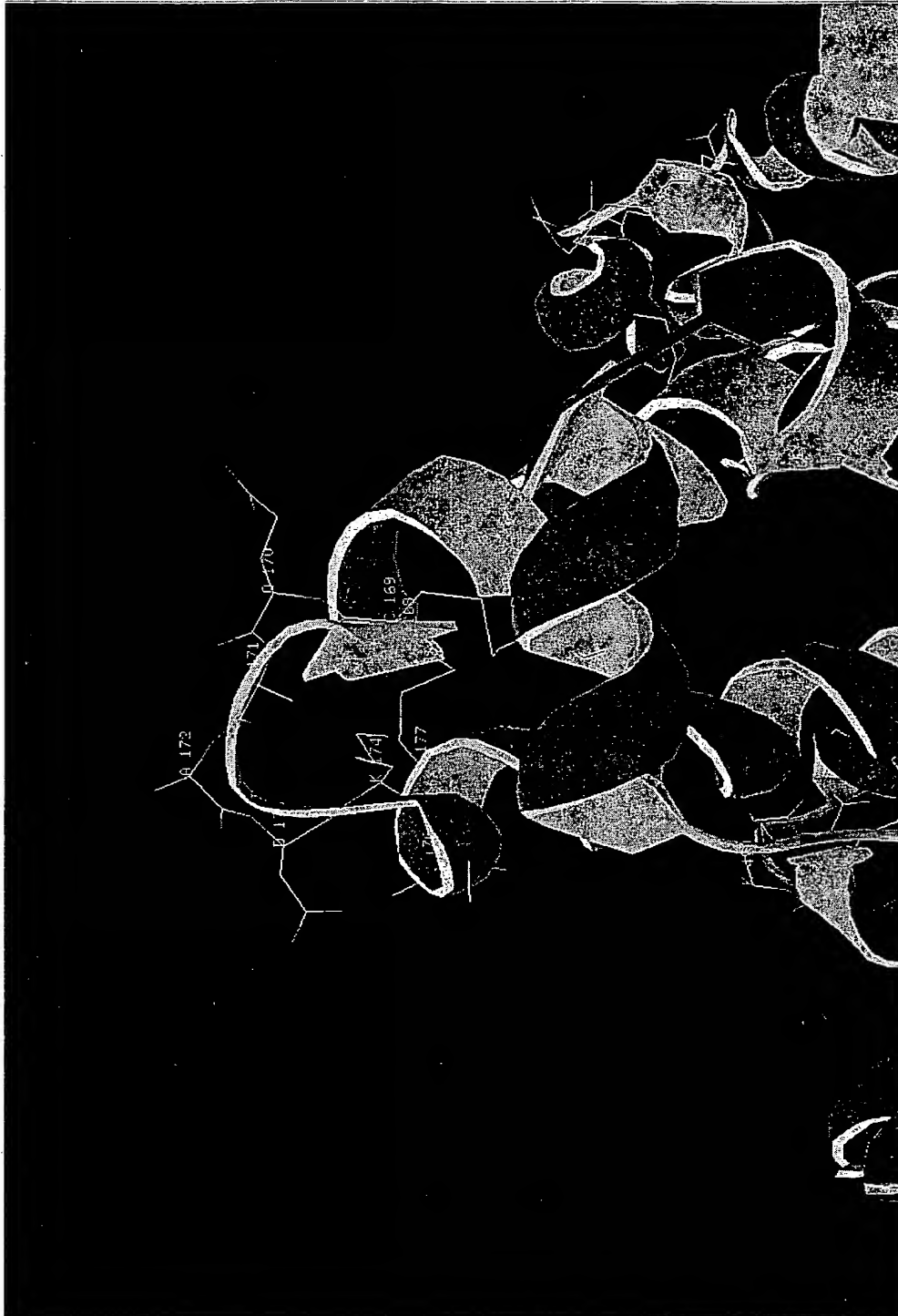


Figure 11

0933118-041201



Disulfide bonds shown in yellow

Figure 12: Loop IV Gln170-Ala176



Figure 13: Tertiary Structure of HA

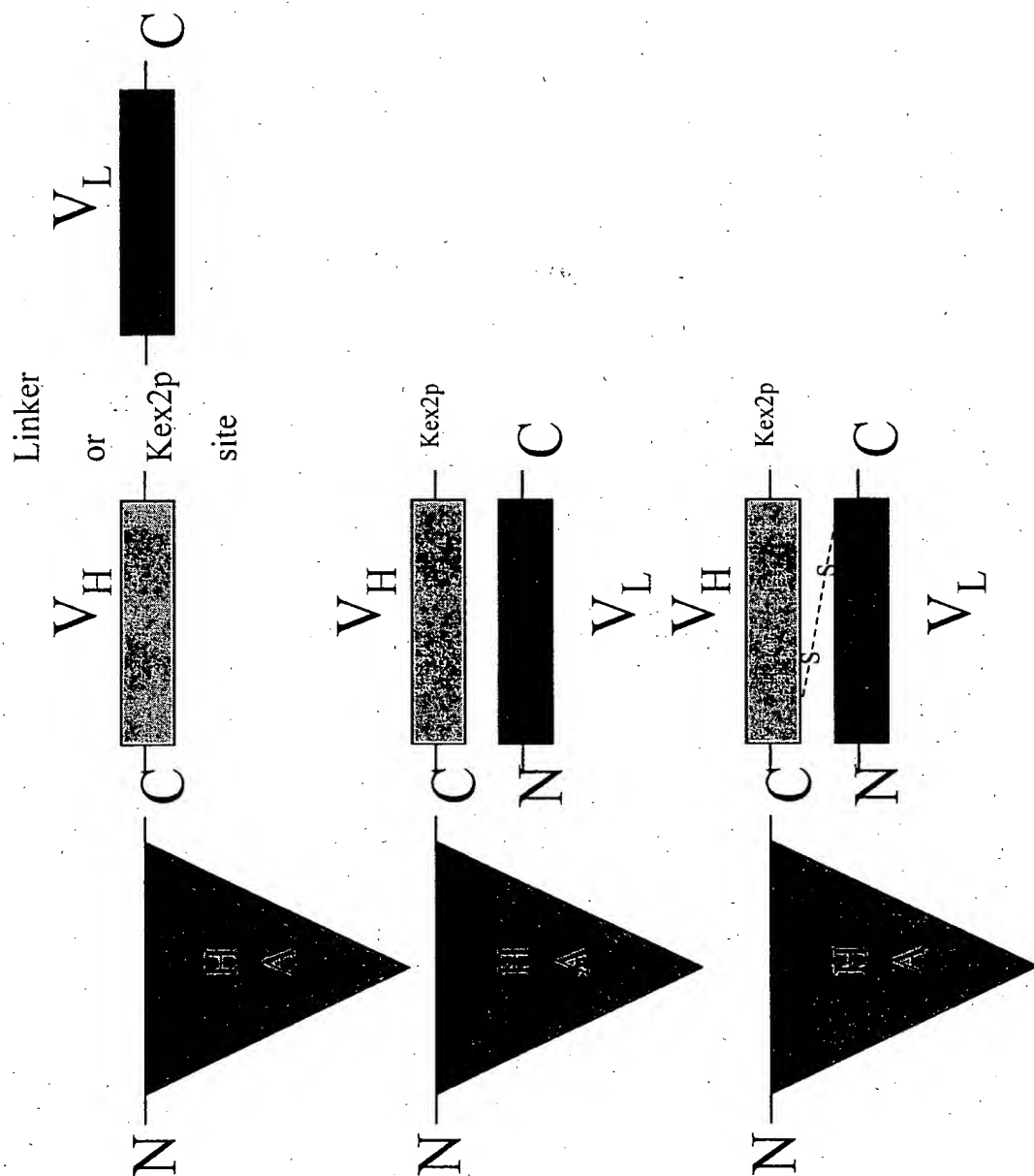


Figure 14: Schematic Diagram of Possible ScFv Fusions
 (Example is of a C-terminal fusion to HA)

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1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
1 D A H K S E V A H R F K D L G E E N F K 20

61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
21 A L V L I A F A Q Y L Q C P F E D H V 40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
41 K L V N E V T E F A K T C V A D E S A E 60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
61 N C D K S L H T L F G D K L C T V A T L 80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
81 R E T Y G E M A D C C A K Q E P E R N E 100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
101 C F L Q H K D D N P N L P R L V R P E V 120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121 D V M C T A F H D N E E T F L K K Y L Y 140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
141 E I A R R H P Y F Y A P E L L F F A K R 160

Figure 15A

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481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
 161 Y K A A F T E C C Q A A D K A A C L L P 180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
 181 K L D E L R D E G K A S S A K Q R L K C 200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
 201 A S L Q K K F G E R A F K A W A V A R L S 220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
 221 Q R F P K A E F A E V S K L V T D L T K 240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
 241 V H T E C C H G D L L E C A D D R A D L 260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
 261 A K Y I C E N Q D S I S S K L K E C C E 280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
 281 K P L L E K S H C I A E V E N D E M P A 300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
 301 D L P S L A A D F V E S K D V C K N Y A 320

Figure 15B

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961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TAC TCT GTC GTG CTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
341 Y S V V L L L R L A K T Y E T L E K C 360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
361 C A A A D P H E C Y A K V F D E F K P L 380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
381 V E E P Q N L I K Q N C E L F E Q L G E 400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
401 Y K F Q N A L L V R Y T K K V P Q V S T 420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC AAC CAG TTA 1380
441 P E A K R M P C A E D Y L S V V L N Q L 460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
461 C V L H E K T P V S D R V T K C C T E S 480

Figure 15C

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1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
 481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
 501 E F N A E T F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
 521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
 541 K E Q L K A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
 561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
 581 A A L G L * 585

Figure 15D